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A cross-sectional study of subjective complaints in patients with epilepsy who seem to be well-controlled with anti-epileptic drugs

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Summary

Objectives: Side-effects of anti-epileptic drugs (AEDs) may be overlooked in patients with epilepsy in everyday clinical practice. The aim of this study was to assess the prevalence and severity of subjective complaints in patients who were considered to be well-controlled and to assess whether these complaints are related to medication, personality traits, or other determinants.
Methods: We included patients with epilepsy who were considered to be well-controlled in a cross-sectional study in seven hospitals in the Netherlands. Their

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medication had not been changed for six months and an apparent reason to change the medication was lacking at the time of enrolment. Subjective complaints were assessed with a 46-item questionnaire. Using multivariable linear regression modeling, we assessed whether patient characteristics, epilepsy characteristics, medication, quality of life (Qolie-10), and personality traits (SCL-90) explained the presence and severity of complaints.

Results: Of 173 included patients, 67% reported moderate to severe subjective complaints on the questionnaire. Cognitive complaints were reported most frequently. Multivariate modeling showed that 61% of the variance in reported complaints could be explained by included determinants. The prevalence and severity of complaints was associated with AED polytherapy and higher scores on psycho neuroticism.

Conclusions: Patients who were considered to be well-controlled proved to report an unexpectedly high number of subjective complaints. Both medication and aspects of personality contributed to the level of complaints. Our study illustrates that subjective side-effects are easily overlooked in everyday clinical practice, possibly because in practice a generally phrased question is used to detect side-effects.

Introduction

The goal of treatment with antiepileptic drugs (AEDs) is to control epileptic seizures without causing side-effects.[1] However, side-effects or subjective complaints may be overlooked easily. Side-effects may start insidiously, patients may not associate their complaints to the medication and identification of for example cognitive complaints or mental slowing may be quite difficult.[2–4] Disregarding side-effects may interfere with the well being of the patients.[2,3,5–7]

Two recent studies showed that complaints attributed to AEDs are frequently overlooked in clinical practice.[2,5] A study by Gilliam et al. showed unexpected, toxic side-effects in 31% of 200 screened patients from outpatient epilepsy clinics. They concluded that systematic screening of side-effects in all patients on AEDs would be useful.[5] A cross-sectional study in pharmacies by our group showed that 60% of patients with epilepsy using AEDs reported one or more complaints on a questionnaire.[2]

Earlier studies did not assess the relation between reported side-effects and AED use or other determinants. Furthermore, the occurrence of side-effects or subjective complaints in patients who seem well-controlled was never assessed.

The aim of this cross-sectional study was to assess the prevalence and severity of subjective complaints in patients with epilepsy who are considered to be well-controlled with AEDs by their treating physician. In addition, we assessed whether these complaints were related to AEDs or other determinants, such as personality traits.

Patients and methods

Patients and setting

Seven hospitals in the Netherlands participated in this cross-sectional study. The medical ethics committees of each participating hospital approved the protocol.

Between October 2002 and July 2005 patients were asked to participate in the study if they were 18 years or older and had well-controlled epilepsy, defined as no medication change in the past six months and no obvious clinical reason to change the medication at the time of inclusion. Patients did not have to be seizure free to be considered well-controlled. We excluded patients with a concurrent disease or disorder that might interfere with the conduct of the study, such as impaired intellectual functioning or other reasons leading to inability to comply with the protocol or complete the necessary questionnaires.

Data

From every patient, age, sex, length and weight was documented, as well as type of epilepsy, aetiology, seizure frequency, time since diagnosis, and time since the last seizure. We recorded the current use of AEDs and the number of AEDs used over the years.

Symptom check list

All patients filled out a questionnaire on psycho neuroticism: the Dutch version of the Symptom Check List (SCL-90),[8,9] to assess the tendency to complain in general.

Quality of life

A brief quality of life questionnaire, specific for epilepsy, was completed (Qolie-10).[10]

The higher the score on the Qolie-10, the better the quality of life. The Qolie-10 includes two questions assessing physical and mental side-effects (''Are you bothered by physical/mental effects of anti-epileptic drugs''). These two questions were separately analysed.

Subjective complaints

Complaints were assessed using a list of 46 items with possible AED-related complaints,[2,5] the SIDAED (Appendix A). The included items form 10 categories: general CNS, behavior (increased irritability), depressive symptoms, cognitive function, motor problems and co-ordination, visual complaints, headache, cosmetic and dermatological complaints, gastrointestinal complaints, and sexuality and menses (Appendix B). For each item the patient rates the severity of the complaint on a four-point Likert scale (no problem, mild, moderate, or serious problem). In addition, the duration of the complaints is scored (since a few weeks, since months or half a year or longer).

Data analysis

A total subjective complaints score was calculated for each patient from the SIDAED complaints questionnaire, consisting of the number of mentioned complaints, weighing a mild score as 1, moderate as 2 and severe as 3 points. Thus, the range of the total complaints score could vary from 0 to 138.

We used univariable and multivariable linear regression modeling with the total weighted complaint score (SIDAED) as the outcome (dependent variable) and patient and epilepsy characteristics, Qolie-10, and SCL-90 as determinants (independent variables). In the multivariable analysis, besides gender, we included determinants that were statistically significantly associated with the outcome in the univariable analysis (p-value <0.05). Since the SCL-90, Qolie-10 and SIDAED may be partly overlapping measures, we repeated the multivariable analysis excluding either the Qolie-10 or the SCL-90.

Additionally, we determined the difference between assessing complaints with a detailed questionnaire or asking a general phrased question, by comparing the findings on the 46-item SIDAED with the two general Qolie-10 questions concerning physical and mental effects of AEDs. For that purpose, the SIDAED was also divided into physical and mental complaints. The categories: motor problems and co-ordination, visual complaints, headache, cosmetic and dermatological complaints, gastrointestinal complaints, and sexuality and menses were combined as physical complaints. The categories general CNS, behavior, depressive symptoms, and cognitive function reflected mental complaints.

All statistical analyses were performed with SPSS version 12.0, Chicago, IL, USA.

Results

Between October 2002 and July 2005, 173 patients were included in the study. Patient characteristics are shown in Table 1. The distribution of subjective complaints as measured by the SIDAED ranged from 0 to 84 (possible range 0—138), with a median of 10. Only nine patients (5%) mentioned no complaints at all (Fig. 1).

The complaints score for each of the 10 categories is shown in Fig. 2. Cognitive dysfunction was mentioned by 78% of patients, 35% reported only mild complaints, 28% (mild and) moderate complaints, and 15% (also) reported severe cognitive complaints. Other categories of complaints that were mentioned by more than half of the patients concerned general CNS, gastrointestinal problems, dermatological or cosmetic problems, and depressive symptoms.

The total weighted complaints score was associated with the quality of life, with psycho neuroticism, with polytherapy, with the time since last seizure, and with the number of used AEDs over the years (Table 2). The linear regression coefficients indicate

Table 1 Patient characteristics ($N = 173$)

Age (years)	48 (±17)
Sex (% men)	50
Body height (cm)	172 (±11)
Body weight (kg)	76 (±14)
Body mass index, BMI (kg/m^2)	26 (±4)
Epilepsy classification (%)	
Localization related	65
Generalized	28
Undetermined	7
Median (range) duration of epilepsy (years)	6 (0—65)
Median (range) number of seizures during the last month	0 (0—180)
Median (range) time since last seizure (years)	2 (0—55)
Number of used AEDs over the years	2.2 (±1.4)
Monotherapy AED (%)	85
Qolie-10 (range 1—5)	4.1 (±0.8)
Median (range) SCL-90 score (range 90—450)	109 (90—307)

Values are mean (±standard deviation) unless otherwise indicated.

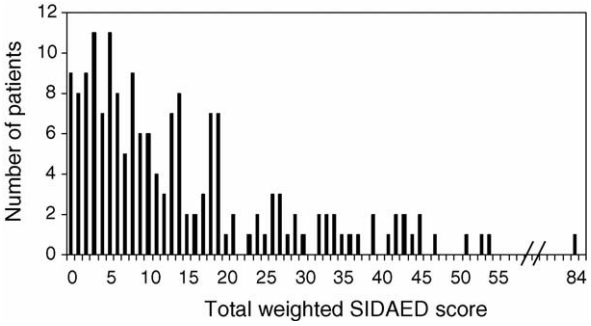

Figure 1 Distribution of total weighted subjective complaints score (SIDAED).

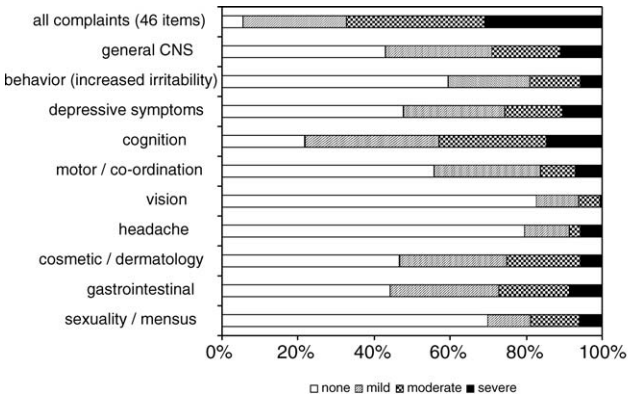

Figure 2 Subjective complaints per category.Patients were counted in the level of highest reported severity, e.g. a patient with moderate and severe problems within one category, was counted as severe.

the change in number of total weighted complaints score with every unit increase of the determinant. Thus, more complaints occurred when more AEDs were used over the years, with use of polytherapy compared to monotherapy, and with higher psycho neuroticism score (SCL-90). Less subjective complaints occurred with increasing time since the last seizure and a low total complaints score was associated with a high quality of life score (Qolie-10).

In the multivariable linear regression analysis, we included the determinants with a high univariable association (p-value <0.05) with the total weighted complaints score as outcome (Table 3). Our choice of possible determinants of subjective complaints seemed appropriate as the total model showed an adjusted R^2 of 61%, leaving only 39% unexplained variance. The SCL-90 score contributed most to the model and the contribution of the Qolie-10 seems to

Table 2 Univariable association between total weighted subjective complaint score and patient and epilepsy characteristics, quality of life, and psycho neuroticism

	Linear regression coefficient	95% CI	*P*-value
Age (years)	0.04	−0.08 to 0.17	0.49
Sex (female versus male)	3.24	−0.93 to 7.42	0.13
Body mass index, BMI (kg/m^2)	−0.40	−0.91 to 0.11	0.13
Localization related epilepsy (yes vs. no)	1.71	−2.57 to 5.99	0.43
Generalized epilepsy (yes versus no)	0.36	−4.46 to 5.19	0.88
Duration of epilepsy (years)	0.06	−0.14 to 0.25	0.58
Number of seizures during the last month	0.02	−0.10 to 0.14	0.71
Time since last seizure (years)	−0.41	−0.76 to −0.06	0.02
Number of used AEDs over the years	1.54	0.02 to 3.07	0.05
Polytherapy AED (yes versus no)	7.50	1.73 to 13.27	0.01
Qolie-10 score	−9.70	−12.00 to −7.40	<0.01
SCL-90 score	0.32	0.29 to 0.36	<0.01

95% CI = 95% confidence interval of linear regression coefficient.

Table 3 Multivariable association between total weighted subjective complaint score and included determinants

	Adjusted R^2	Linear regression coefficient	95% CI	*P*-value
Model	0.61			
Sex (female/male)		2.06	−0.79 to 4.90	0.16
Time since last seizure (years)		−0.07	−0.40 to 0.07	0.16
Number of used AEDs		0.54	−0.64 to 1.72	0.37
Polytherapy (yes/no)		3.85	−0.61 to 8.30	0.09
Qolie-10 (score)		−0.28	−2.70 to 2.11	0.82
SCL-90 (score)		0.30	0.25 to 0.35	<0.01

95% CI = 95% confidence interval of linear regression coefficient.

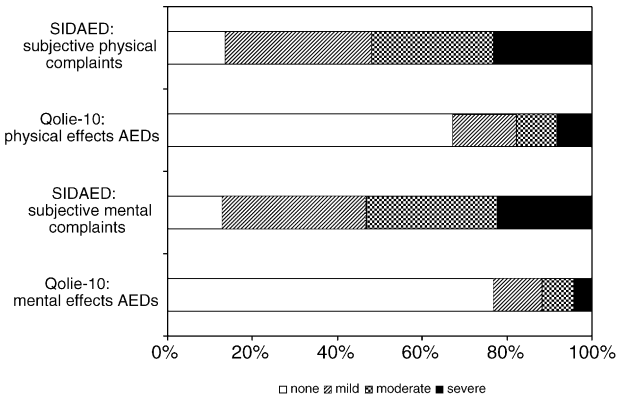

Figure 3 Reported subjective complaints (SIDAED) and physical and mental effects of AEDs (Qolie-10).For the SIDAED, patients were counted in the level of highest reported severity, e.g. a patient with moderate and severe problems on the physical or mental categories was counted as severe.

be overlooked in the multivariable model, which may be due to partial overlap of the Qolie-10 and the SCL-90. When the SCL-90 score was excluded from the multivariable analysis, the adjusted R^2 decreased to 30% and polytherapy still contributed to the complaints score (p-value 0.05) as well as the Qolie-10 score with a linear regression coefficient of -8.62 (95% confidence interval -11.13 to -6.11) and a p-value <0.01.

Assessing subjective complaints with the SIDAED and reporting physical and mental effects of AEDs on the Qolie-10 differed substantially (Fig. 3). In total, 95% of patients mentioned complaints on the SIDAED, of whom 116 (67%) at least one moderate or severe complaint. On the other hand, on the Qolie-10 only 33% of the patients mentioned physical side-effects from AEDs (18% moderate to severe) and only 23% mentioned mental side-effects from AEDs (11% moderate to severe).

Discussion

Our study shows that 67% of patients who were considered well-controlled reported subjective complaints. Cognitive complaints were most frequently mentioned. The two most important factors related to reported complaints were medication use, i.e. whether the patient used mono- or polytherapy, and personality traits, i.e. higher scores on psycho neuroticism.

The patient characteristics of our population are in agreement with what we expected of patients with well-controlled epilepsy, continuing on the same AED for years: 28% of our study population was over 60 years of age, patients were diagnosed with epilepsy a long time ago and most patients received monotherapy.

The percentage of patients with moderate to severe subjective complaints concur with the study by Carpay et al. (67% versus 60%).[2] However, Carpay et al. focused on all patients using AEDs in a certain community, regardless of whether the seizures were under control or not, while we assessed seemingly well-controlled patients, using AEDs for many years.[11] Gilliam et al. assessed the prevalence of toxic side-effects of AEDs in patients, selected from an outpatient epilepsy clinic with severe epilepsies, probably with a worse seizure control compared to our study population.[5] These studies already indicated that systematic screening for side-effects of AEDs or complaints associated with AED use probably will improve the well being of patients, as was also suggested in an editorial based on the paper by Gilliam et al.[6] Our results show that in seemingly well-controlled patients, reported subjective complaints are unexpectedly high and that systematic screening can be useful to detect these complaints.

In clinical practice, the physician will ask the patient whether there are any problems regarding the medication. Since our patient population is considered well-controlled, we may conclude that most patients will answer with no. Asking a more specific question, like in the Qolie-10: "Are you bothered by physical/mental effects of anti-epileptic drugs?", detects moderate to severe problems in one-third of these patients. Checking whether patients subjectively experience side-effects through a thorough list of specific complaints, covering a number of domains (as in the SIDAED), revealed complaints in two-third of the patients. This may indicate that patients often do not associate experienced complaints with their chronic AED use, resulting in an under detection of AED side-effects related complaints in every day clinical practice, which again stretches that systematic screening can be useful.

Most of the variation in subjective complaints, as measured by the SIDAED, was explained by the determinants included in our models, especially polytherapy and psycho neuroticism. We expect that the type of AED may be part of the 39% unexplained variance of complaints. In a subsequent trial we will assess whether changing the medication in patients reporting subjective complaints has a positive effect on the reported complaints and on quality of life.

Cognitive complaints and general CNS reactions were mentioned frequently. Also when we take the number of items per category into account, complaints were most frequently mentioned in these two categories. This is in agreement with earlier studies.[2,7,12] Although the epilepsy itself may cause memory deficit and therefore cognitive

complaints,[13,14] studies have shown that memory impairment is multifactorial and that AEDs can reduce memory performance.[14] Furthermore, the age of the participants did not play a role in reported cognitive complaints, since there was no association found between age and reported complaints, even when we only analyzed cognitive complaints (p-value 0.24).

We are aware that the SIDAED complaints questionnaire measures subjective complaints, which is not the same as a neuropsychological assessment method. However, our purpose was to assess the daily routine in normal clinical practice, where neuropsychological assessments are usually not performed in well-controlled patients. For the treating physician, it will be more informative to know whether the patient suffers from certain subjective complaints than to have exact neuropsychological information, especially when changing medication might remedy these subjective complaints.

We chose not to include a control group to assess subjective complaints in people that do not use AEDs. Possibly, subjective complaints from the SIDAED list will be reported in other populations, even in healthy ones. However, for our purpose, which was to assess subjective complaints in well-controlled patients with epilepsy using AEDs, this was less relevant. Furthermore, the distribution of mentioned complaints concurs to what we expected in our research population.[2,7,12]

The weights to assess the severity of the mentioned complaints were arbitrarily applied. However, changing the applied weights to 1, 3 and 5 instead of 1, 2 and 3 for mild, moderate and severe, respectively, yielded the same results: SCL-90 and polytherapy still had the strongest association with the total weighted subjective complaints score.

The SCL-90, measuring psycho neuroticism, contributed most to the model explaining the presence of complaints, which reflects the general association between emotional lability and a tendency to complain. However, the "patient with well-controlled epilepsy" is not more neurotic than the standard population, since the SCL-90 score of our population did not differ from the norm population.[9]

The Qolie-10 (quality of life) and the SCL-90 (psycho neuroticism) probably are partly overlapping measures. This may explain the non-significant contribution of the Qolie-10 in the multivariable model that also included the SCL-90. After exclusion of the SCL-90, the Qolie-10 contributes significantly to the model (p-value <0.01), confirming a partial overlap between the two measures.

In conclusion, our results indicate that in clinical practice complaints among patients with epilepsy who are considered well-controlled by their physician are very common. Both treatment characteristics and aspects of personality contribute to the presence and severity of complaints. The question whether patients experience side-effects from their medication is not the same as asking specifically for certain complaints and systematic screening to detect subjective complaints can be useful in daily clinical practice.

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Appendix A. SIDAED list of subjective complaints

1	I have problems with my gums
2	I have lost weight
3	I have difficulty remembering names
4	I often feel drowsy and sleepy
5	I sometimes have to hold on to something to stop myself from falling
6	I forget all sorts of things, such as appointments
7	I find it hard to concentrate
8	I tire easily and have little energy
9	I am easily aggressive
10	I can only concentrate on something for short periods
11	I constantly walk into tables, doorposts etc.
12	I feel agitated and restless
13	I notice my reaction to others is slow
14	I cannot concentrate on the same thing for long periods of time
15	I notice my speech is slow
16	I constantly feel pressurized and excitable
17	I often suffer from dizzy spells
18	I have little appetite
19	My periods are irregular
20	I notice I sometimes have difficulty expressing myself
21	I often feel nauseous
22	I worry all day
23	I often suffer from diarrhea
24	My hands shake all the time
25	I have surplus saliva
26	I often suffer from double vision
27	I suffer from skin rash or other skin problems
28	I have gained weight
29	I think more slowly than I used to
30	I am easily irritated
31	I feel depressed and miserable
32	My bowel movement is often difficult
33	I have difficulty finding the right words
34	I am becoming less and less active

Appendix A (*Continued*)

35	I cannot get to sleep and often lie awake
36	I am less often in the mood for sex
37	Sometimes I cannot do anything because of headaches
38	I suffer from hair loss
39	My vision is blurred
40	My hair growth has increased
41	When I want to pick up something, my hands start shaking
42	I do not feel capable of performing normal my daily activities
43	I often suffer from headaches
44	Making love has become less pleasant
45	I often suffer from stomach trouble
46	I often feel light-headed

Severity was stated as no problem/mild/moderate/serious problem. Duration was stated as since a few weeks/months/half a year or longer.

Appendix B. SIDAED questionnaire items per category

Category	Included items
General CNS	4, 8, 14, 42
Behavior (increased irritability)	9, 12, 16, 30
Depressive symptoms	22, 31, 34, 35
Cognitive function	3, 6, 7, 10, 13, 15, 20, 29, 33
Motor problems and co-ordination	5, 11, 17, 24, 41, 46
Visual complaints	26, 39
Headache	37, 43
Cosmetic and dermatological complaints	1, 25, 27, 38, 40, 45
Gastrointestinal complaints	2, 18, 21, 23, 28, 32
Sexuality and menses	19, 36, 44

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